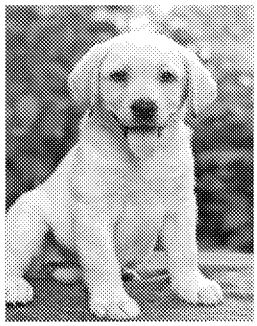
Seresto and EPA's Regulation of Pet Products



2021

Briefing for the OPP-IO

Melanie Biscoe, Jackie Herrick, HED placeholder

Jackie

Purpose

- The purpose of this briefing is to:
  - Present OPP's regulation of pet products.
  - Provide an update on efforts to broadly address pet risk in OPP.
  - Discuss proposals to address incidents reported on the collar Seresto.

Jackie

U.S. Pet Product Regulation

- EPA regulates products applied directly to pets such as spot-ons, collars, shampoos, sprays, dips.
- In addition to typical data requirements, these products are supported by efficacy studies and a companion animal safety study.
  - The guideline for the companion animal safety study has not been updated in ~20 years and these studies are usually negative for adverse effects.
  - Small sample sizes and use of known hardy breeds detract from usefulness of these studies.
- Currently, both EPA and FDA have statutory responsibility in regulating products used on pets.
  - EPA regulates pet products applied to exterior of animals that are ***"not systemic."***
- **Ex. 5 Deliberative Process (DP)**

Jackie

FDA and EPA Regulation of Pet Products

	Current EPA Requirements	Current FDA Requirements
Pre-market Animal Safety Study	Guideline No: 870.7200 Title: Companion Animal Safety Number of Animals: 6 per sex per dose Level of Concern: 5X Other: Harmonized with previous FDA/CVM Guidance #33	Guideline No: 185 (VICH GL43) Title: Target Animal Safety for Veterinary Pharmaceutical Products Number of Animals: 4 per sex per dose Level of Concern: 5X Other: International harmonization
Pre-market Clinical Trials	None	Guideline No: 85 (VICH GL9) Title: Good Clinical Practice Number of Animals ~200 (where 1/2 are positive control). Represents populations of actual pets rather than only test beagles. Informs labeling and contributes to the overall approval decision.
Post-market Surveillance	Aggregate summary reporting of summary numbers of adverse effects under FIFRA Section 6(a)(2). Generally only used to trigger a more detailed review.	Ten veterinarians and other professional staff evaluate detailed adverse events, particularly for new products. Findings may result in changes to product, label, insert, and communication with vets and the public.

Melanie

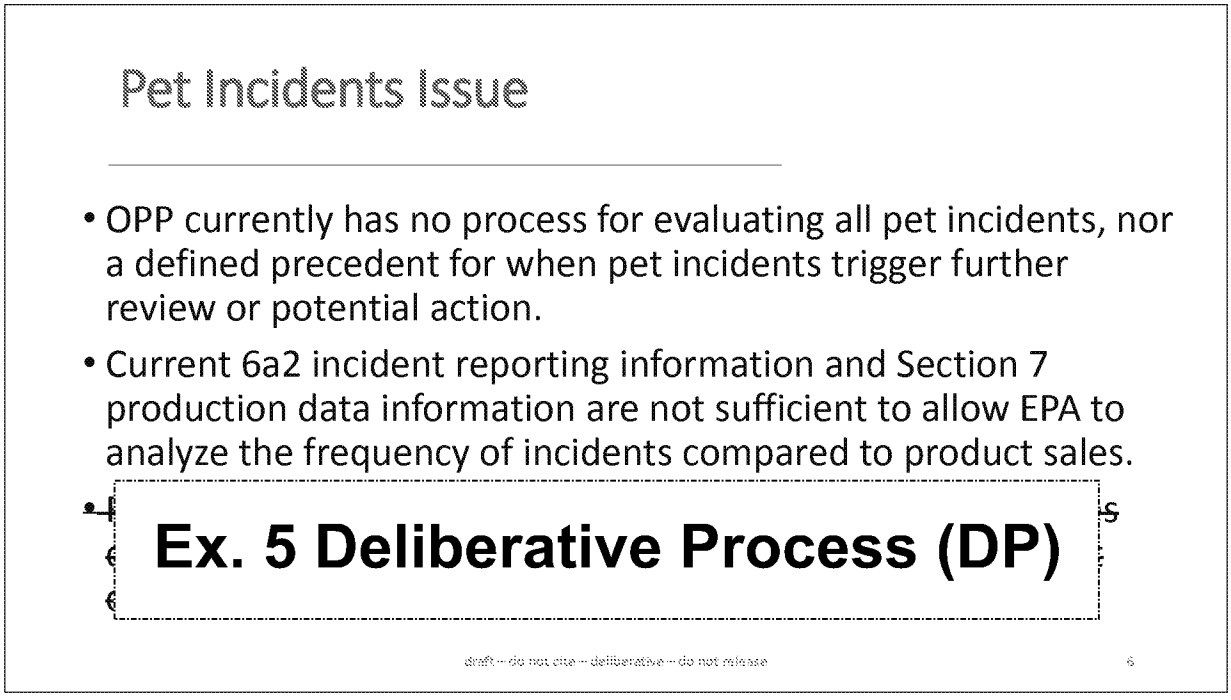
History of EPA Mitigation of Spot ons

- In 2009, due to an increase in reports of pet incidents involving spot-on pesticide products, OPP implemented the following measures:
  - 2-year time-limited conditional registrations.
  - Label mitigation to clarify instructions for safe use and provide clear indicators to prevent misuse.
  - Limitation on CSFs to one formulation.
  - Enhanced quarterly incident reporting with corresponding sales data (such as exposure scenarios and associated clinical signs).
- In 2018 OPP and 5 companies concluded a pilot using uniform templates for enhanced reporting.
  - Efforts are currently underway to request all registrants to submit their reporting in this new form.
  - As an incentive to report in the new form, EPA has agreed to remove the 2-year time-limitation registration and convert the reporting requirement from quarterly to annual.

Jackie

Ex. 5 Deliberative Process (DP)

Conclusions of pilot are still pending



Melanie
In Registration Review, PIDs and IDs discuss ongoing efforts to review incidents, but to date we have not published pet incident data in our decision documents.

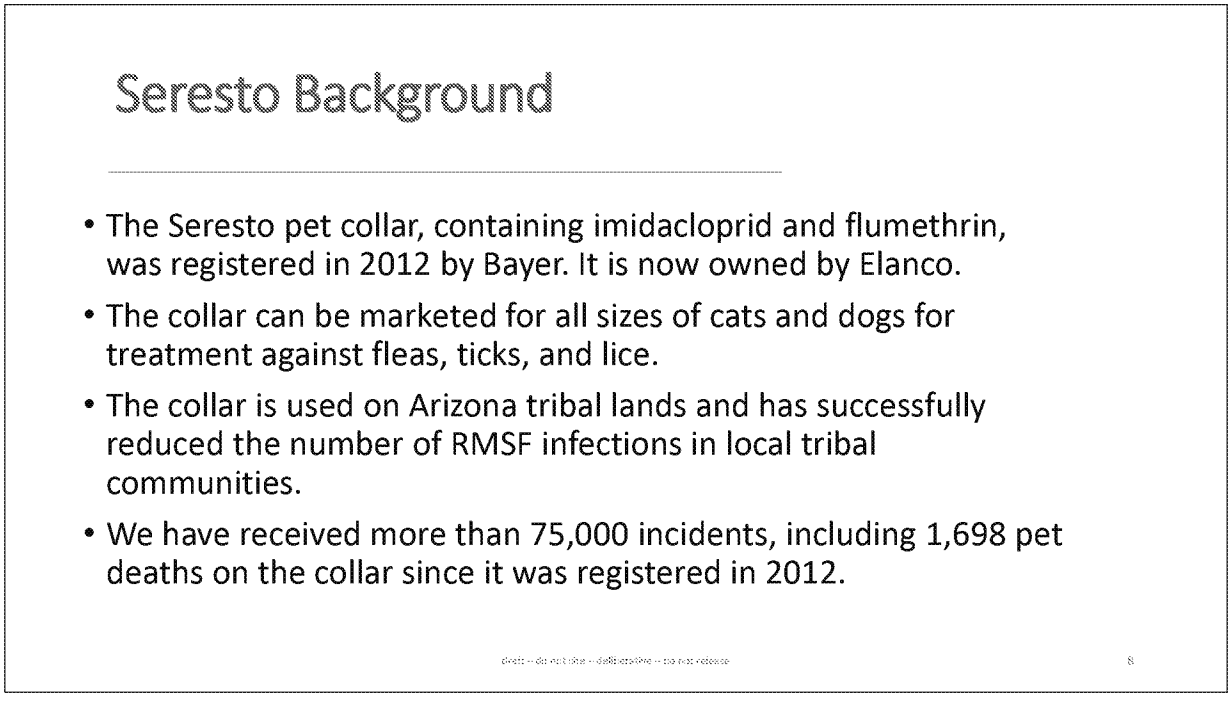
Pet Incidents Issue

- In Registration Review, potential human health risks of concern have been identified from use on pets for several chemicals (e.g., fipronil, amitraz) currently being evaluated. Regulatory actions based on pet incidents should not drive consumers toward products with potential human health risks of concern.
- In March 2019 the OPP OD was briefed on team recommendations for cross-product review of pet incident information, prompting Ex. 5 Deliberative Process (DP)

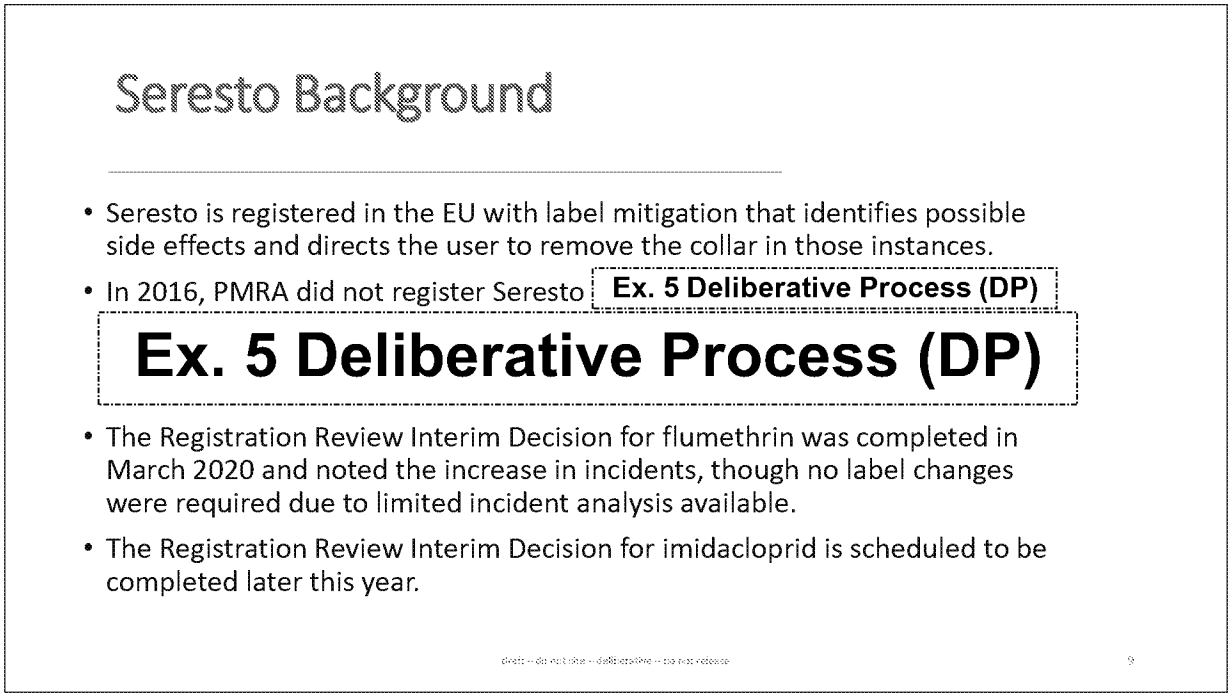
Ex. 5 Deliberative Process (DP)

Melanie

review could be a mechanism for action on pet products, but is currently not used in this manner



Jackie
EU: In rare cases behavioural disorders that may include hiding, vocalization, hyperactivity, excessive licking and/or grooming or scratching at the application site may be observed in animals that are not used to wearing collars on the first few days after fitting. Aggression after collar application was reported in very rare cases. Ensure that the collar is fitted correctly. Application site reactions such as pruritus, erythema and hair loss may occur. These have been reported as rare and usually resolve within 1 to 2 weeks. In single cases, a temporary collar removal may be recommended until the symptoms have disappeared. In very rare cases, application site reactions such as dermatitis, inflammation, eczema, lesions or haemorrhage may occur and in these instances, collar removal is recommended. In rare cases neurological symptoms as ataxia, convulsions and tremor may occur. In these cases collar removal is recommended. Also in rare cases in dogs slight and transient reactions as depression, change of food intake, salivation, vomiting and diarrhea might occur initially. The frequency of adverse reactions is defined using the following convention: -very common (more than 1 in 10 animals treated displaying adverse reaction(s)) -common (more than 1 but less than 10 animals in 100 animals treated) -uncommon (more than 1 but less than 10 animals in 1,000 animals treated) -rare (more than 1 but less than 10 animals in 10,000 animals treated) -very rare (less than 1 animal in 10,000 animals treated, including isolated reports)



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PMRA Analysis

PMRA conducted an Incident Analysis on US Incidents from 2012-2015 during their review of an application to register the product in Canada. In this review, PMRA had access to US sales data. EPA only received the draft report which indicated the following:

- Seresto incidents were reported at a rate of **36 to 65 per 10,000** collars sold.
- PMRA considers an incident rate greater than **1 per 10,000** units sold an indicator of a potential problem
- The average rate of incidents of 15 other collars was **0.7 per 10,000** collars sold.
- The report predominantly addressed the incidents that were assessed as "Possible" or "Probable."
- PMRA's human health assessment also identified potential human health risks of concern.

Jackie

OPP's Pet Incident Analysis

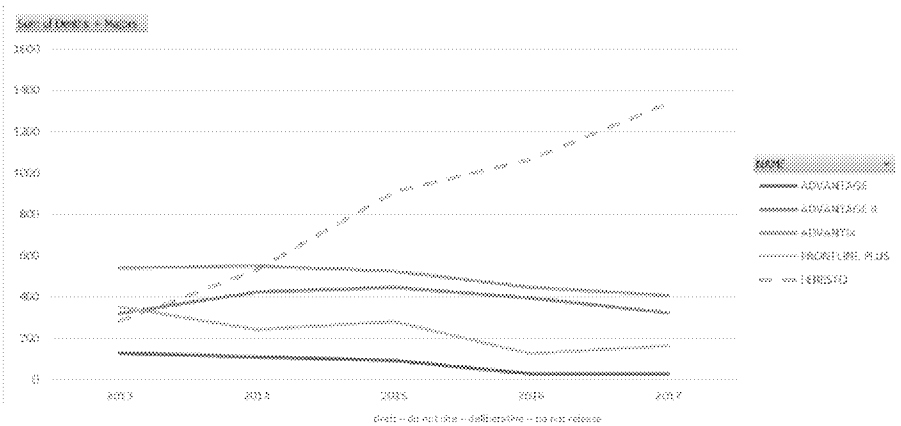
All OPP analyses shown on the following slides are internal and have not been made available to the public

Tier	Data Source	Description
Level 0: Aggregate Incident Data System Query	OPP's Incident Data System	• Descriptive analysis will be performed using OPP's Incident Data System (IDS). • IDS captures data on domestic animal (pet) incidents received under FIFRA 6(a)(2) from registrants and is reported in aggregate form on a quarterly basis.
Level 1: Reporting Odds Ratio (ROR)	OPP's Incident Data System	• Comparison of disproportionality of severe outcomes (typically death and major) across pet products of interest • Can be estimated with existing data but may be biased due to differential reporting across products (e.g., Under-Reporting, Stimulated Reporting, Weber Effect)
Level 2: Incident Rate Ratio (IRR)	OPP's Incident Data System Enhanced Reporting Data on Units Sales	• Comparison of the rate of a given outcome (typically death and major) for one product to the rate of (same) outcome to another. • Estimation of rates requires sponsor to submit sales data.
Level 3: Signal-Based Case-by-Case Review & Causality Analysis	Enhances Reporting Data and Narrative Information	• Signal-based case-by-case review evaluates cases on an individual basis and incorporates information in the submitted narrative • This may involve investigating IRR on a symptom rather than a product basis and may incorporate causality analysis.

HED

OPP Incident Comparison of Select Bayer Products

Death + Major incidents per year by major product (all products combined for cat/dog, all sizes)



draft – do not cite – deliberative – do not release

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HED
Incident data alone show there are more incidents for seresto when compared to other bayer products. Shows why people are concerned – this is the only information we typically see that there may be an issue

OPP ROR Analysis (2014-2015)

- **Reporting Odds Ratio** – the odds of an incident of one product compared to the odds for other products
- Advantage II for Dogs, Seresto and K9 Advantix had higher incidence rates of death+majors relative to other Bayer products. (ROR>1)
- K9 Advantix for Dog had significantly higher incident rates of deaths than other Bayer products.
- Advantage II for Cats and Advantage II for Dogs also had higher incident rates of deaths relative to other Bayer products.

Table 1. Reporting Odds Ratio (ROR) Analysis

Comparison A product vs. all other products	Death + Major + Moderate + Minor Cases	Death		Death + Major	
		Cases	ROR (95%ci)	Cases	ROR (95%ci)
Advantage II for Cats	5396	130	1.16 (0.96, 1.40)	423	0.93 (0.83, 1.03)
Advantage®II for Dogs	2324	78	1.66 (1.31, 2.11)	295	1.67 (1.47, 1.90)
K9 Advantix II for Dogs	11956	217	0.79 (0.67, 0.92)	735	0.63 (0.58, 0.69)
K9 Advantix for Dogs	239	34	7.92 (5.47, 11.46)	48	2.80 (2.04, 3.86)
Seresto	**15,444**	**296**	**0.83 (0.71, 0.96)**	**1,438**	**1.26 (1.17, 1.36)**

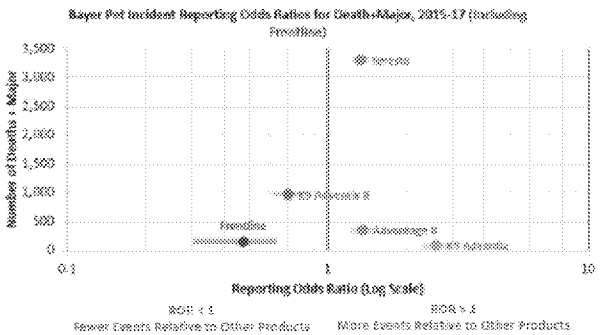
HED

At the same time, HED conducted some analyses on the available data.
-Seresto isnt the only product with incident issues – all other products compared here are spot ons.

OPP ROR Analysis (2015-2017)

Level 1: Reporting Odds Ratio (ROR)

ROR analysis of Seresto and other Bayer products (+ Frontline).



- **Similar outcome when HED updated their analysis a few years later.**

HED

OPP IRR Analysis (2014-2015)

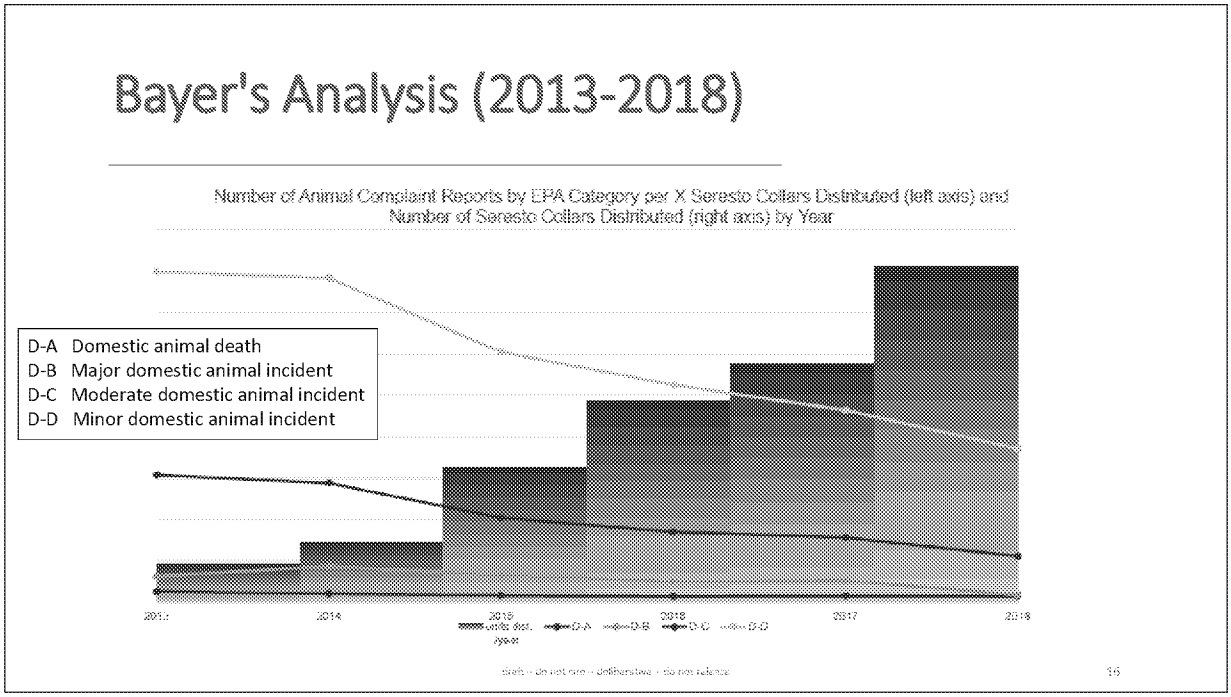
- **Incidence Rate Ratios –** Analysis of the number of pet incidents compared to the sales volume and the reapplication interval of the product (IRR>1)
- Seresto and K9 Advantix had higher incidence rates of deaths and majors compared to other Bayer products during 2014-2015.
- K9 Advantix for Dog had significantly higher incident rates of deaths than other Bayer products.
- Updated sales data were not available for HED to re-run the analysis in 2017

Table 2. Incidence Rate Ratio (IRR) Analysis

Comparison A product vs. all other products	Death Incidents		Death + Major Incidents	
	Cases	IRR (95% CI)	Cases	IRR (95% CI)
Advantage II for Cats	130	0.73 (0.60, 0.88)	423	0.59 (0.53, 0.65)
Advantage®II f or Dogs	78	0.88 (0.70, 1.12)	295	0.86 (0.76, 0.96)
K9 Advantix II for Dogs	217	0.64 (0.55, 0.75)	735	0.53 (0.49, 0.58)
K9 Advantix for Dogs	34	14.14 (10.03, 19.95)	48	4.98 (3.74, 6.62)
Seresto	**296**	**1.71 (1.47, 1.97)**	**1438**	**2.53 (2.36, 2.72)**

HED

Important: Seresto incidents were normalized to a "pet-month" unit for comparison to spot ons with shorter durations. This made the calculated IRR less conservative for Seresto – less than half of symptoms occurred in less than 2 months. A straight comparison would lead to IRRs for Seresto 40 times greater than K9 advantix.



HED

This is all bayer gave us – we don't have the data that support this graph and they wouldn't give it to us.
Even if we get seresto sales data, we wouldn't have data for other collars to compare

Current Seresto Issue

- We continue to receive reports of pet incidents.
  - In 2019, 384 pet deaths were recorded.
  - Neurological signs and seizures anecdotally appear to be related to the collar's use
- In March 2021, USA Today published an article after receiving an aggregate incident report via FOIA.
  - As of 3/17 there have been 2 Congressional inquiries on the incidents since the article published.
  - 75,000 incidents, 1698 pet deaths, and nearly 1000 human incidents over 8 years.
- **We need sales data and additional incident details to give context to the incident numbers.**

Jackie
*Elanco stated they did not think they could submit incident data electronically so were holding off on paper submissions until we returned to the office.

Recommended Next Steps

1. Ex. 5 Deliberative Process (DP)

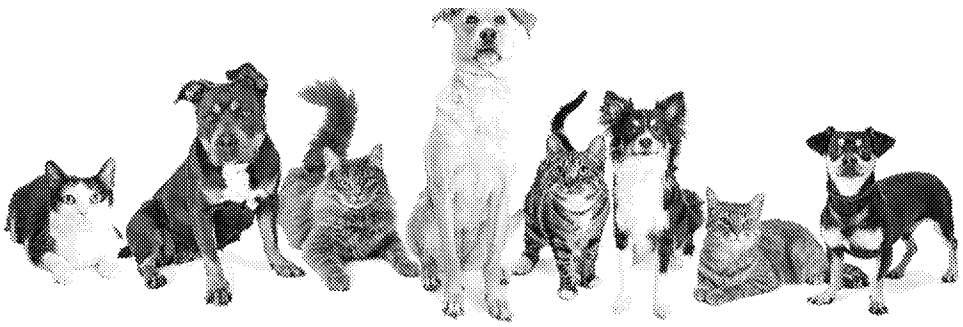
2. **Regulatory Options for Seresto**
   a. **Get Seresto sales data and detailed data on neurological symptoms found in incidents, then analyze in conjunction with 6a2 incident data. OPP could acquire Seresto data by:**
      a. Requesting that Elanco provide it voluntarily
      b. Issuing 6a2 letter requiring it
      c. Issuing a Data Call-In (DCI) requiring it (OMB review is needed for this option)
   b. **Ex. 5 Deliberative Process (DP)**

For all Seresto-specific options, Elanco likely will push back that EPA is unfairly targeting its product

Jackie
Potential label mitigation: S Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP)

Data considerations:
When do we anticipate to receive the data?
Who would review the data? How would OPP evaluate and implement?
We do not currently have a standard that details how many incidents are needed to determine this product is unsafe.

As of 2018, 178 of the 417 registered pet products (43%) are from spot-ons which are already required to submit enhanced reporting data, while an additional 40 products (10%) are collars. The remaining pet products (47%) are dips, sprays, otic applications, tags, powders, shampoos, and wipes. However, over 90% of all pet incidents reported are from collar and spot-on applications.



Thank You! Questions?

EU Label Language

Source: Product leaflet from the EU Head of Medicines Agency
https://mri.cts-mrp.eu/Human/Downloads/DE_V_0143_004_FinalPL.pdf

6. ADVERSE REACTIONS

In rare cases behavioural disorders that may include hiding, vocalization, hyperactivity, excessive licking and/or grooming or scratching at the application site may be observed in animals that are not used to wearing collars on the first few days after fitting. Aggression after collar application was reported in very rare cases. Ensure that the collar is fitted correctly.
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-rare (more than 1 but less than 10 animals in 10,000 animals treated)
-very rare (less than 1 animal in 10,000 animals treated, including isolated reports)

If you notice any side effects, even those not already listed in the package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

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Melanie
EU: